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Is Graft-versus-Leukemia More Effective Using Reduced-Intensity Conditioning Compared with Myeloablative Conditioning?

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Allogeneic hematopoietic stem cell transplantation (HSCT), an established therapy for treatment of leukemia and other hematologic malignancies, is the most effective way to demonstrate that the immune system may control cancer. The so-called "graft-versus-leukemia" (GVL) effect has been demonstrated in experimental animals and in several clinical studies [1]. From the clinical studies, it seems that chronic graft-versus-host disease (GVHD) has a more potent GVL effect than acute GVHD [1,2]. However, GVHD is associated with high morbidity and mortality, and in several studies the best long-term leukemia-free survival (LFS) was seen in patients with mild acute and mild chronic GVHD [1,3].

The aim of myeloablative conditioning (MAC) before HSCT is to kill as many leukemic cells as possible and rescue the patient with a hematopoietic graft from a healthy donor. A limitation of MAC is toxicity to several organs. Reduced-intensity conditioning (RIC) was introduced to overcome some of the toxicity induced by MAC and allow the use of HSCT in elderly patients and those with comorbidities who otherwise would not be candidates for HSCT [4]. RIC is less dependent on the antitumor effect of high-dose chemoradiotherapy and takes advantage of the GVL effect induced by immunocompetent cells in the healthy donor graft. Donor lymphocyte infusion can further potentiate the GVL effect [5].

In this issue of *Biology of Blood and Marrow Transplantation*, Weisdorf and colleagues from the Center for International Blood and Marrow Transplant Research (CIBMTR) compare the GVL effect in more than 5000 patients with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) who underwent HSCT with a MAC or RIC regimen [6]. This is the largest study of GVL comparing MAC and RIC published to date.

The patients were divided into 4 groups: those without GVHD, those with acute GVHD alone, those with chronic GVHD alone, and those with both acute and chronic GVHD. In the first analysis, all patients were included, and acute and chronic GVHD were treated as time-dependent covariates. Multivariate analysis identified a decreased likelihood of relapse associated with both MAC and RIC in patients with chronic GVHD only and those with both acute and chronic GVHD. However, among patients with acute GVHD only, those who received RIC had a significantly lower probability of relapse ($P < .0001$) compared with those who received MAC, in whom acute GVHD only had no impact on the probability of relapse ($P = .16$). This finding suggests that acute GVHD should be avoided in patients receiving MAC, but mild or moderate acute GVHD may be beneficial in patients treated with RIC. In both MAC and RIC recipients, transplantation-related mortality (TRM) was increased in all patients with any form of GVHD ($P < .0001$). Taken together, these findings indicate that an increased impact of GVHD on relapse and TRM (ie, treatment failure) in patients with acute GVHD only who received either MAC or RIC. However, in patients with acute and chronic GVHD, treatment failure was increased in those receiving MAC (hazard ratio [HR] 1.5; $P < .0001$), but not in those treated with RIC (RR, 1.19; $P = .11$). This significant finding suggests that patients with acute and chronic GVHD have improved LFS when conditioned with RIC, but not when conditioned with MAC. This may be because MAC is more toxic, and thus may be associated with more critical and severe GVHD as opposed the acute and chronic GVHD in patients treated with RIC.

Survival was decreased in patients with acute GVHD only regardless of whether they were treated with MAC or RIC ($P < .0001$). In the MAC recipients, survival did not differ significantly between those with

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chronic GVHD only and those without GVHD ($P = .90$). However, in the RIC recipients, survival was improved in those with chronic GVHD only (HR, 0.74; $P = .007$). In the patients with acute and chronic GVHD, MAC was associated with decreased survival (HR, 1.37; $P < .0001$). In contrast, in RIC recipients, there was no statistically significant difference in survival between those without GVHD and those with both acute and chronic GVHD (HR, 1.13; $P = .22$).

This large study demonstrates that the GVL effect is more effective in RIC recipients by reducing treatment failure and improving survival in comparison with MAC recipients. This is a modern material with a large cohort of patients and so must be taken seriously. Of course, some caution is necessary, given this study's limitations typically associated with retrospective multicenter studies.

The second analysis was a landmark analysis of more than 2000 patients who survived at least 1 year disease-free after HSCT. In the MAC recipients, no GVL effect of acute or chronic GVHD was evident in any of the 3 GVHD groups. In contrast, RIC recipients with both acute and chronic GVHD had a significantly reduced probability of relapse (HR, 0.44; $P = .009$). In this landmark analysis, TRM was increased in all MAC recipients with any form of GVHD, but only in RIC recipients with both acute and chronic GVHD ($P = .002$). Taken together, these findings indicate increased treatment failure in MAC recipients with chronic GVHD only and with both acute and chronic GVHD. In the RIC recipients, 1-year disease-free survivors in all of the GVHD groups demonstrated no increase in treatment failure compared with those without GVHD. Overall survival was decreased in the MAC recipients with chronic GVHD only ($P = .0001$) and with both acute and chronic GVHD ($P < .0001$). In contrast, overall survival was not significantly different in RIC recipients without GVHD and those with acute GVHD only or chronic GVHD only, but was decreased in those with both acute and chronic GVHD ($P = .018$).

This study suggests that the GVL effect is stronger and less harmful with RIC, not only in survivors during the first year after HSCT, but also in those living disease-free after 1 year posttransplantation. Thus, the long-term GVL effect is apparently more beneficial with RIC as opposed to MAC. Several large registry studies that compared outcomes in patients with AML and MDS who received MAC or RIC found essentially lower TRM and an increased relapse rate in RIC recipients compared with MAC recipients, similar LFS and survival in the 2 groups [7-9].

As Weisdorf et al. show, RIC seems to be associated with a stronger GVL effect, with less toxicity and suffering in the early posttransplantation period. Because LFS and survival do not differ in patients treated with RIC or MAC, RIC may be preferred over MAC in patients in remission. In MAC recipients, no beneficial effects of acute and chronic GVHD on improving LFS or survival were noted compared with patients without GVHD [6]. A GVL effect occurs in the absence of acute GVHD; thus, GVHD probably should be avoided in patients receiving MAC [1]. However, the grade of acute and chronic GVHD was not considered in the present analysis, and the possibility remains that mild acute and chronic GVHD are beneficial in HSCT recipients treated with MAC, as reported previously [1]. HSCT without severe acute GVHD can be achieved through T cell depletion of the graft or long-term immunosuppression with anti–T cell immunoglobulin [1]. However, T cell depletion is associated with increased risk of leukemic relapse unless conditioning is intensified [1,10]. It is also possible to induce mild acute and mild chronic GVHD by giving low-dose cyclosporine and then discontinue immunosuppression after 3-4 months in the absence of GVHD, as has been done in recipients of HLA-identical sibling transplants [11]. This approach resulted in increased mild acute GVHD, increased probability of chronic GVHD, decreased leukemic relapse, and improved LFS and survival. According to the present CIBMTR study, this approach may be even more successful and safer in recipients of RIC.

Several previous studies have reported a reduced probability of acute and chronic GVHD with RIC compared with MAC [7,12]. One explanation for this finding may be that toxicity induced by the regimen triggers and paves the way for GVHD [1,13-15]. From the present CIBMTR study, it seems that acute and/or chronic GVHD that does occur is better tolerated by RIC recipients than by MAC recipients [6].

In conclusion, this large CIBMTR study suggests that the GVL effect in patients with AML or MDS is more optimal—that is, results in improved survival and LFS (both short-term and long-term)—when using RIC as opposed to MAC. The data suggest that RIC should be selected more often as conditioning for good-risk patients with AML and MDS. A prospective randomized study is warranted to confirm these data.

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Immune Recovery after Allogeneic Hematopoietic Stem Cell Transplantation: Is It Time to Revisit How Patients Are Monitored?

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Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is associated with deficiencies in T and B cell reconstitution that can persist for over a year and have been linked to increased risks of infections [1-4], disease relapse [5], and the development of secondary malignancies [6]. Posttransplantation immune reconstitution is affected by several factors, including thymic involution associated with advanced patient age, the conditioning regimen, HLA disparity between donor and recipient, T cell depletion of the graft, occurrence of graft-versus-host disease (GVHD), and the drugs used to prevent or treat GVHD. Total body irradiation (TBI), for example, decreases the production of IL-7 by thymic stromal cells, suggesting that radiation may affect normal T cell regeneration driven by IL-7 [7]. In addition, approaches used to prevent GVHD through in vivo (with alemtuzumab or antithymocyte globulin, ATG) or in vitro T cell depletion also have a significant impact on T cell recovery [1,8-17]. Finally, GVHD has been shown to affect the thymus [18-20], and also has a significant impact on immune recovery due to immunosuppressive drugs required to treat GVHD [21-26].

Different approaches have been used to assess posttransplantation immune recovery, from relatively simple and readily available parameters such as absolute lymphocyte count (ALC) or counts of lymphocyte subsets ($CD4^+$ and $CD8^+$ T cells, NK cells, B cells), to more complex and less routine assays of T cell repertoire and T cell receptor–expressing circles (TRECs) [1-4,15-18,27-30]. ALC has been shown to be predictive of overall survival and relapse in several studies [15,27-30], whereas $CD4^+$ T cell count has been shown to correlate with an increased risk of fatal opportunistic infections [1,16]. Studies of TRECs, which can be used as markers of thymopoiesis, have shown more rapid recovery in younger recipients and in recipients of conventional grafts compared to T cell–depleted grafts [17], whereas the occurrence of

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